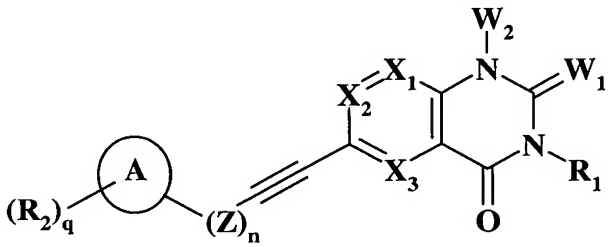
CLAIMS

What is claimed is:

1. A combination, comprising a selective inhibitor of COX-2 that is not celecoxib or valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13 of Formula (A)



(A)

or a pharmaceutically acceptable salt thereof, or an N-oxide thereof,

wherein:

W_1 is O, S, or NR_3, wherein R_3 is hydrogen, $(C_1\text{-}C_6)$alkyl, hydroxyl or cyano;

W_2 is selected from :

hydrogen;

trifluoromethyl;

NH_2;

$(C_1\text{-}C_{10})$alkylN(H);

$[(C_1\text{-}C_{10})\text{alkyl}]_2N$, wherein each $(C_1\text{-}C_{10})$alkyl moiety is the same or different;

$(C_1\text{-}C_6)$alkyl;

$(C_3\text{-}C_6)$alkenyl;

$(C_3\text{-}C_6)$alkynyl;

phenyl;

naphthyl;

phenyl-$(C_1\text{-}C_{10})$alkyl;

naphthyl-$(C_1\text{-}C_{10})$alkyl;

$(C_3\text{-}C_{10})$cycloalkyl-$(C_1\text{-}C_{10})$alkyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

a nonaromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 3 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

wherein in W_2 each (C_1-C_{10})alkyl, (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, phenyl, naphthyl, phenyl-(C_1-C_{10})alkyl, naphthyl-(C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl-(C_1-C_{10})alkyl, aromatic heterocycle, and nonaromatic heterocycle group is independently unsubstituted or substituted by from 1 to 3 groups, which may be identical or different, selected from halo, NH_2, (C_1-C_{10})alkylN(H), [(C_1-C_{10})alkyl]$_2$N, wherein each (C_1-C_{10})alkyl moiety is the same or different, cyano, trihalo(C_1-C_6)alkyl, (C_1-C_6)acyl, C(=O)OR_4, -OR_4, and SR_4;

R_4 is hydrogen or (C_1-C_6)alkyl; or

W_2 and W_1 may be taken together to form a diradical group W_2-W_1 of formula W_3=X_4-N;

W_3 is N or CR_5 wherein R_5 is selected from:

hydrogen;

OR_6;

SR_6;

(C_1-C_6)alkyl;

(C_3-C_8)cycloalkyl;

a saturated heterocycle comprising from 3 to 8 ring members which are carbon atoms and one heteroatom selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

phenyl;

naphthyl;

(C_5-C_{10})heteroaryl comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

phenyl-(C_1-C_{10})alkyl; and

naphthyl-(C_1-C_{10})alkyl;

R_6 is selected from hydrogen, (C_1-C_6)alkyl, phenyl-(C_1-C_{10})alkyl, and naphthyl-(C_1-C_{10})alkyl;

wherein in W_3 each (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, saturated heterocycle, phenyl, naphthyl, (C_5-C_{10})heteroaryl, phenyl-(C_1-C_{10})alkyl, and naphthyl-(C_1-C_{10})alkyl group is independently unsubstituted or substituted by $(CH_2)_p$-OH or $(CH_2)_p$-NH_2;

p is an integer of from 0 to 4 inclusive;

X_4 is N or CR_7, wherein R_7 is selected from:

hydrogen;

NR_8R_9;

OR_8;

SR_8;

(C_1-C_6)alkyl;

(C_3-C_8)cycloalkyl;

a saturated heterocycle comprising from 3 to 8 ring members which are carbon atoms and one heteroatom selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

phenyl;

naphthyl;

(C_5-C_{10})heteroaryl comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

phenyl-(C_1-C_{10})alkyl; and

naphthyl-(C_1-C_{10})alkyl;

R_8 and R_9 are the same or different, and are selected from hydrogen; (C_1-C_6)alkyl; phenyl-(C_1-C_{10})alkyl; and naphthyl-(C_1-C_{10})alkyl;

wherein in X_4 each (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, saturated heterocycle, phenyl, naphthyl, (C_5-C_{10})heteroaryl, phenyl-(C_1-C_{10})alkyl, and naphthyl-(C_1-C_{10})alkyl group is independently unsubstituted or substituted by $(CH_2)_p$-OH or $(CH_2)_p$-NH_2, wherein p is an integer from 0 to 4 inclusive;

X_1, X_2 and X_3 independently of each other are N or C-R, wherein R is selected from:

hydrogen;

$(C_1$-$C_6)$alkyl;

hydroxyl;

$(C_1$-$C_6)$alkoxy;

halo;

trifluoromethyl;

cyano;

nitro;

$S(O)_{n1}R_4$, wherein R_4 is as defined above;

$NR_{10}R_{11}$;

n_1 is an integer of from 0 to 2 inclusive;

R_{10} and R_{11} are the same or different, and are independently selected from

hydrogen;

$(C_1$-$C_6)$alkyl;

phenyl-$(C_1$-$C_{10})$alkyl; and

naphthyl-$(C_1$-$C_{10})$alkyl; or

R_{10} and R_{11} may be taken together with the nitrogen atom to which they are bonded to form a 5-membered or 6-membered ring containing carbon atoms, the nitrogen atom to which R_{10} and R_{11} are attached, and optionally a second heteroatom selected from O, S, N(H), and N$(C_1$-$C_{10})$alkyl,

wherein not more than two of the groups X_1, X_2, and X_3 simultaneously are a nitrogen atom;

n is an integer of from 0 to 8 inclusive;

Z is $C(R_{12})(R_{13})$;

Each R_{12} and R_{13} independently of each other are selected from:

hydrogen;

$(C_1$-$C_6)$alkyl;

trihalo$(C_1$-$C_6)$alkyl;

halo;

NH_2;

$(C_1$-$C_6)$alkylN(H);

$[(C_1$-$C_6)$alkyl$]_2$N, wherein each $(C_1$-$C_6)$alkyl moiety is the same or different;

OR_4;

SR_4; and

$C(=O)OR_4$, wherein R_4 is as defined above; or

R_{12} and R_{13} on the same carbon atom may be taken together with the carbon atom to which they are attached to form a carbonyl group; and

Z can contain 1 carbon-carbon double bond when two R_{12} groups are absent and n is an integer of from 2 to 8; and

Z can contain 2 carbon-carbon double bonds when four R_{12} groups are absent or three R_{12} and one R_{13} groups are absent and n is an integer of from 3 to 8; and

Z can contain 1 carbon-carbon triple bond when two each of R_{12} and R_{13} are absent and n is an integer of from 2 to 8; and

Z can contain 2 carbon-carbon triple bonds when four each of R_{12} and R_{13} are absent and n is an integer of from 4 to 8; and

One $C(R_{12})(R_{13})$ group in Z can be replaced with O, N(H), $N(C_1$-$C_6)$alkyl, S, S(O), or $S(O)_2$;

A is selected from:

phenyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-$(C_1$-$C_{10})$alkyl;

a nonaromatic 5-membered or 6-membered monocycle comprising carbon atoms and from 0 to 4 heteroatoms selected from O, S, N(H), and N-$(C_1$-$C_{10})$alkyl;

naphthyl;

an aromatic 8-membered to 12-membered bicycle comprising two aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 1 to 6 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

an aromatic 8-membered to 12-membered bicycle comprising one aromatic 5-membered or 6-membered ring and one non-aromatic 5-membered or 6-membered ring, wherein the rings may be bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 6 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl; and

a non-aromatic 8-membered to 12-membered bicycle comprising two non-aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 4 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

Each R_2 may be the same or different, and is independently selected from:

hydrogen;

(C_1-C_6)alkyl;

halo;

cyano;

nitro;

trihalo(C_1-C_6)alkyl;

$NR_{10}R_{11}$;

OR_{14};

SR_{14};

$S(O)R_{14}$;

$S(O)_2R_{14}$;

(C_1-C_6)acyl;

$(CH_2)_kNR_{10}R_{11}$;

$X_5(CH_2)_kNR_{10}R_{11}$;

$(CH_2)_kSO_2NR_{14}R_{15}$;

$X_5(CH_2)_kC(=O)OR_{14}$;

$(CH_2)_kC(=O)OR_{14}$;

$X_5(CH_2)_kC(=O)NR_{14}R_{15}$;

$(CH_2)_kC(=O)NR_{14}R_{15}$; and

X_6-R_{16};

X_5 is O, S, N(H), or N(C_1-C_6)alkyl;

k is an integer of from 0 and 3 inclusive;

R_{10} and R_{11} are as defined above;

R_{14} and R_{15} may be the same or different, and independently are hydrogen or (C_1-C_6)alkyl;

X_6 is a single bond, -CH_2-, O, or S, S(O), or $S(O)_2$;

R_{16} is selected from:

phenyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

cyclopentyl;

cyclohexyl; and

a nonaromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 3 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

wherein in R_{16} each phenyl, aromatic 5-membered or 6-membered, heterocyclic ring, cyclopentyl, cyclohexyl, and non-aromatic 5-membered or 6-membered heterocyclic ring group independently is unsubstituted or substituted with from 1 to 3 groups independently selected from (C_1-C_6)alkyl, halo, trihalo(C_1-C_6)alkyl, hydroxyl, (C_1-C_6)alkoxy, SH, (C_1-C_6)alkylthio, NH_2, (C_1-C_6)alkylN(H), [(C_1-C_6)alkyl]$_2$N, wherein each (C_1-C_6)alkyl moiety may be the same or different;

q is an integer of from 0 to 7 inclusive;

R_1 is a group selected from:

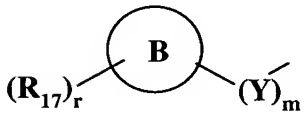
hydrogen;

$(C_1\text{-}C_6)$alkyl;

$(C_3\text{-}C_6)$alkenyl; and

$(C_3\text{-}C_6)$alkynyl,

wherein in R_1 each $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$alkenyl, and $(C_3\text{-}C_6)$alkynyl group is independently unsubstituted or substituted with from 1 to 3 groups independently selected from NH_2, $(C_1\text{-}C_6)$alkylN(H), $[(C_1\text{-}C_6)\text{alkyl}]_2N$, wherein each $(C_1\text{-}C_6)$alkyl moiety may be the same or different, $(C_1\text{-}C_6)$alkyl, cyano, trihalo$(C_1\text{-}C_6)$alkyl, $C(=O)OR_4$, OR_4, SR_4, wherein R_4 is as defined above, and a group of formula (1)



(1)

m is an integer of from 0 to 8 inclusive,

Y is $CR_{18}R_{19}$;

Each R_{18} and R_{19} independently of each other, is selected from:

hydrogen;

$(C_1\text{-}C_6)$alkyl;

phenyl;

trihalo$(C_1\text{-}C_6)$alkyl;

halo;

NH_2;

$(C_1\text{-}C_6)$alkylN(H);

$[(C_1\text{-}C_6)\text{alkyl}]_2N$, wherein each $(C_1\text{-}C_6)$alkyl moiety may be the same or different;

OR_4;

SR_4; and

$C(=O)OR_4$;

R_4 is as defined above;

Y can contain 1 carbon-carbon double bond when two R_{18} groups are absent and m is an integer of from 2 to 8; and

Y can contain 2 carbon-carbon double bonds when four R_{18} groups are absent or three R_{18} and one R_{19} groups are absent and m is an integer of from 3 to 8; and

Y can contain 1 carbon-carbon triple bond when two each of R_{18} and R_{19} are absent and m is an integer of from 2 to 8; and

Y can contain 2 carbon-carbon triple bonds when four each of R_{18} and R_{19} are absent and m is an integer of from 4 to 8; and

One $C(R_{18})(R_{19})$ group in Y can be replaced with O, N(H), N(C_1-C_6)alkyl, S, S(O), or $S(O)_2$;

B is a group selected from:

phenyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

a nonaromatic 5-membered or 6-membered monocycle comprising carbon atoms and from 0 to 4 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

naphthyl;

an aromatic 8-membered to 12-membered bicycle comprising two aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 1 to 6 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

an aromatic 8-membered to 12-membered bicycle comprising one aromatic 5-membered or 6-membered ring and one non-aromatic 5-membered or 6-membered ring, wherein the rings may be bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 6 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl; and

a non-aromatic 8-membered to 12-membered bicycle comprising two non-aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 4 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

r is an integer of from 0 to 7 inclusive,

Each R_{17} may be the same or different and independently is selected from:

hydrogen;

(C_1-C_6)alkyl;

halo;

cyano;

nitro;

trihalo(C_1-C_6)alkyl;

$NR_{10}R_{11}$;

OR_{14};

SR_{14};

$S(O)R_{14}$;

$S(O)_2R_{14}$;

(C_1-C_6)acyl;

$(CH_2)_kNR_{10}R_{11}$;

$X_5(CH_2)_kNR_{10}R_{11}$;

$(CH_2)_kSO_2NR_{14}R_{15}$;

$X_5(CH_2)_kC(=O)OR_{14}$;

$(CH_2)_kC(=O)OR_{14}$;

$X_5(CH_2)_kC(=O)NR_{14}R_{15}$;

$(CH_2)_kC(=O)NR_{14}R_{15}$; and

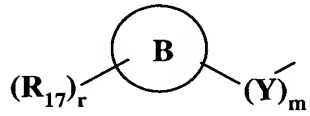
X_6-R_{16}, wherein X_5, k, R_{10}, R_{11}, R_{14}, R_{15}, X_6, and R_{16} are as defined above.

2. The combination of Claim 1, wherein:

W_2 is $(C_1\text{-}C_6)$alkyl;

W_1 is O; and

$R_1$is a group of formula (1)



(1)

wherein Y, B, R_{17}, m, and r are as defined for Formula (A) in Claim 1.

3. The combination of Claim 1, wherein the compound of Formula (A) is selected from:

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin -3-ylmethyl}-benzoic acid methyl ester;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid;

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin -3-ylmethyl}-benzoic acid;

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-benzyl-7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl}-benzoic acid methyl ester;

4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid; and

4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin -3-ylmethyl)-benzoic acid;

or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

4. The combination of Claim 1, wherein the compound of Formula (A) is selected from:

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin -3-ylmethyl}-benzoic acid methyl ester;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid;

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin -3-ylmethyl}-benzoic acid;

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-benzyl-7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl}-benzoic acid methyl ester;.

4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid; and

4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin -3-ylmethyl)-benzoic acid.

5. A pharmaceutical composition, comprising a combination of a selective inhibitor of COX-2 that is not celecoxib or valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

6. A method of treating a disease or disorder selected from cartilage damage, inflammation, arthritis, and pain in a mammal, comprising administering

to the mammal a therapeutically effective amount of a combination of a selective inhibitor of COX-2 that is not celecoxib or valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

7. The method according to Claim 6, wherein the disease or disorder is rheumatoid arthritis.

8. The method according to Claim 6, wherein the disease or disorder is osteoarthritis.

9. The method according to Claim 6, wherein the disease or disorder is joint inflammation.

10. The method according to Claim 6, wherein the pain is joint pain.